Regarding the Claim Amendments

Support for the claim amendments can be found throughout the specification. In particular, the amendment to claims 1 and 2 to recite a Rhesus D antigen "set forth as SEQ ID NO:41" is supported, for example, by Figure 2 and page 27, lines 12-17, which disclose Rhesus D antigen SEQ ID NO:41. Thus, as the amendment to claims 1 and 2 is supported by the specification no new matter has been added. Furthermore, the amendment places the claims in better condition for allowance or appeal. Accordingly, entry of the amendment is respectfully requested.

I. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 1 to 12, 14 and 48 to 51 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Examiner maintains that the specification allegedly does not provided enablement for the full scope of the claims.

The specification adequately enables the claims for the reasons set forth in Applicants Response filed February 25, 2002. Nevertheless, solely in order to further prosecution of the subject application and to place the claims in better condition for allowance of appeal, claims 1 and 2 have been amended to recite that the nucleic acid molecule carrying at least one missense mutation is as compared to the wild type Rhesus D antigen "set forth as SEQ ID NO:41."

As to amended claims 1 and 2 and depending claims 3 to 12, 14 and 48 to 51, the Examiner acknowledges that the specification enables "a nucleic acid molecules comprising SEQ ID NO:41 encoding a human Rhesus D antigen contributing to or indicative of a weak D phenotype." [see, for example, the Office Action at page 2, paragraph 7] Thus, in view of the amendment, claims 1 to 12, 14 and 48 to 51 are adequately enabled. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking enablement be withdrawn.

The rejection of claims 1 to 12, 14 and 48 to 51 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed had possession of the claimed invention, is respectfully traversed. The Examiner maintains that

allegedly the specification does not provide an adequate written description of the nucleic acid molecules, vectors, methods oligonucleotides and kits of the claims.

The specification provides an adequate written description of the claims for the reasons set forth in Applicants Response filed February 25, 2002. Nevertheless, solely in order to further prosecution of the subject application and to place the claims in better condition for allowance of appeal, claims 1 and 2 have been amended to recite that the nucleic acid molecule carrying at least one missense mutation is as compared to the wild type Rhesus D antigen "set forth as SEQ ID NO:41."

As to amended claims 1 and 2 and depending claims 3 to 12, 14 and 48 to 51, the Examiner acknowledges that the specification adequately describes "SEQ ID NO:41 encoding a human Rhesus D antigen carrying the missense mutation." [see, for example, the Office Action at page 8, second paragraph] Thus, in view of the amendment, claims 1 to 12, 14 and 48 to 51 are adequately described. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking enablement be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §102 and 103(a)

The rejection of claims 1, 2, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by Westhoff *et al.* (Blood 83:3098 (1994)) is respectfully traversed. The Examiner indicates that Westhoff *et al.* allegedly describe "a polynucleotide (Accession number A46368) that encodes a human Rhesus D antigen (isolated from K562 cells) carrying one missense mutation at the amino acid position 218 which is within the amino acid position from 114 to 149 as recited in instant claim 2 and does not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or threonine in position 283 by isoleucine." Westhoff *et al.* also allegedly describe that "oligonucleotides that hybridize under stringent conditions to the reference polynucleotide carrying missense mutation or the complementary thereof."

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir. 1990).

Applicants first wish to point out that A46368 is a compilation of several sequences. A46368 corresponds to gi:423065, and contains an Ile at position 218 (see Exhibit 1, submitted

herewith). The correct database sequence for Westhoff *et al.* is S70174 and not A46368 (see Exhibit 2, submitted herewith).

Applicants regret that the remarks distinguishing Westhoff *et al.* from the claimed invention in the previously filed Response have been misunderstood by the Patent Office. The point is this: the alleged missense mutation at amino acid position 218 described by Westhoff *et al.* (Met) is NOT a missense mutation but is instead a wild type sequence. This was corroborated by previously submitted Exhibit B (Cartron *et al.* Transfus. Clin. Biol. 6:497 (1996), in which the authors indicate that a previously described RHD gene sequence with Ile at position 218 resulted from a sequence error. Again, the authors of previously submitted Exhibit B state that "Position 218 is probably not affected since resequencing of D indicates presence of Met218 rather than Ile218 as previously described" (see previously submitted Exhibit B, Table 2 footnote +). Previously submitted Exhibit B therefore unequivocally demonstrates that the Ile residue at position 218 was caused by a sequence error, and that the correct residue at position 218 is Met.

To further corroborate that Met at position 218 is wild type, submitted herewith as Exhibit 3 is a Table of the first 10 sequence hits for RhD in the sequence database. Significantly, A46368 is the only RhD sequence with Ile indicated at position 218; all nine other RhD sequences have Met at position 218. As discussed in detail above and in Applicants' previous Response, Ile at position 218 resulted from a sequence error. Exhibit 3 therefore corroborates that the correct residue at position 218 is Met.

Thus, because Westhoff *et al.* describe Rhesus D sequence having Met at position 218, which is a wild type sequence and NOT a sequence having a missense mutation, as required by the claims, Westhoff *et al.* do not teach or suggest the claimed nucleic acid molecules. Accordingly, Westhoff *et al.* do not teach or suggest the claimed invention, prior to the present amendment and as amended herein. As such, Applicants respectfully request that the rejection of claims 1, 2, 9 and 14 under 35 U.S.C. §102(b) over Westhoff *et al.* (Blood 83:3098 (1994)) be withdrawn.

The rejection of claims 1 to 4, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) is respectfully traversed. The Examiner indicates that Cherif-Zahar *et al.* describe "a polynucleotide (Accession number A30405) that encodes a Rhesus D antigen carrying at least one missense mutation .... at the

amino acid position range from 179-225 as recited in instant claim 2." As to claim 3, Cherif-Zahar *et al.* are indicated to describe "the missense mutation in the reference polynucleotide cause by an amino acid substitution at position at 182, 198 and 223." As to claim 4, Cherif-Zahar *et al.* are indicated to describe "missense mutation in the reference polynucleotide causes by an amino acid substitution at position 182 to Thr, at position 198 to Asn, at position Val." As to claims 9 and 14, Cherif-Zahar *et al.* allegedly describe that "the reference polynucleotide is genomic DNA" and "oligonucleotides (primers) that hybridize to the reference polynucleotide or a portion thereof and the complementary thereof carrying missense mutation."

Cherif-Zahar *et al.* (Accession number A30405) do not teach or suggest the claimed invention. For example, *inter alia*, Cherif-Zahar *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen as required by amended claims 1 and 2. Rather, Accession number A30405 is an RHCE sequence. Nor does Cherif-Zahar *et al.* teach or suggest a nucleic acid molecule encoding a human rhesus D antigen with a missense mutation, let alone a missense mutation contributing to or indicative of the weak D phenotype.

To corroborate Applicants' position that Cherif-Zahar *et al.* do not teach or suggest a nucleic acid molecule encoding a human rhesus D antigen, let alone a human rhesus D antigen with a missense mutation, submitted herewith as Exhibit 4 is an alignment between RHCE A30405 (query) and RhD SEQ ID NO:41 (Sbjct). The alignment reveals that the sequences are different from each other.

Accordingly, as Cherif-Zahar *et al.* do not describe the claimed nucleic acid molecules, Cherif-Zahar *et al.* can not anticipate claims 1 to 4, 9 and 14. As such, Applicants respectfully request that the rejection of claims 1 to 4, 9 and 14 under 35 U.S.C. §102(b) over Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) be withdrawn.

The rejection of claims 10 to 12, 14, 50 and 51 under 35 U.S.C. §103(a) as allegedly unpatentable over Westhoff *et al.* or Cherif-Zahar *et al.* each in view of Sambrook *et al.* (Molecular Cloning, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17) is respectfully traversed. The Examiner indicates that the secondary reference of Sambrook *et al.* adds the limitations missing from the primary cited references as to claims 10 to 12 and 14, thereby allegedly rendering these claims obvious.

Claims 10 to 12, 14, 50 and 51 would not have been obvious in view of any of Westhoff *et al.*, Cherif-Zahar *et al.* and Sambrook *et al.* alone, or in any combination, prior to the present amendment, and as presently amended. As set forth above, Westhoff *et al.* do not describe a nucleic acid encoding a Rhesus D antigen carrying a missense mutation, let alone SEQ ID NO:41 having a missense mutation contributing to or indicative of the weak D phenotype. Cherif-Zahar *et al.* describe an RHCE sequence (Accession number A30405), but do not teach or suggest a nucleic acid encoding a Rhesus D antigen carrying a missense mutation, let alone SEQ ID NO:41 having a missense mutation contributing to or indicative of the weak D phenotype.

The secondary citation of Sambrook *et al.* fails to provide that which is missing from Westhoff *et al.* or Cherif-Zahar *et al.* In particular, Sambrook *et al.* do not teach or suggest a nucleic acid molecule encoding a human Rhesus D antigen. Nor do Sambrook *et al.* teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation. Finally, Sambrook *et al.* do not teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype, let alone SEQ ID NO:41 having a missense mutation contributing to or indicative of the weak D phenotype.

Thus, absent any teaching or suggestion of the invention of claims 10 to 12, 14, 50 and 51 the claims would not have been obvious at the time of the invention in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection of claims 10 to 12, 14, 50 and 51 under 35 U.S.C. §103(a) be withdrawn.

The rejection of claim 48 under 35 U.S.C. §103(a) as allegedly unpatentable over Westhoff *et al.* or Cherif-Zahar *et al.* each in view of Sambrook *et al.* (Molecular Cloning, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17) and further in view of U.S. Patent No. 6,200,802 (the '802 patent) is respectfully traversed. The Examiner indicates that the '802 patent adds the limitation missing from the other cited references thereby allegedly rendering claim 48 obvious.

Claim 48 depends from claim 14 which, as set forth above, would not have been obvious in view of any of Westhoff *et al.*, Cherif-Zahar *et al.* and Sambrook *et al.* alone, or in any combination, prior to or as presently amended.

The '802 patent fails to provide that which is missing from Westhoff *et al.*, Cherif-Zahar *et al.* and Sambrook *et al.* In particular, for example, the '802 patent does not teach or suggest a nucleic acid molecule encoding a human Rhesus D antigen, a nucleic acid molecule encoding a human RHD antigen having a missense mutation, a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype; nor SEQ ID NO:41 having a missense mutation contributing to or indicative of the weak D phenotype.

Absent any teaching or suggestion of the invention of claim 48, the claims would not have been obvious at the time of the invention in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection of claim 48 under 35 U.S.C. §103(a) over Westhoff *et al.*, Salvignol *et al.*, Cherif-Zahar *et al.* in view of U.S. Patent No. 6,200,802 be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 12, 14 and 48 to 51 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

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